Dignam

**Acidosis** – Decreased urea production, increased NH4 excretion (70% vs 30% normally)

**Ammonia toxicity** – high levels of NH4 leads to:

1. Increased glucagon -> gluconeogenesis increase in kidney -> increased NH4
2. Increased glucose due to gluconeo -> increased insulin -> increased uptake of BCAA -> increased NH4
3. Increased uptake of Ca/Na ions in neural NMDA receptors leads to:
4. Increased Na/K ATPase activity to offset Na flux
5. Ca binds calcineurin which activates Na/K ATPase
6. Decreased ATP synthesis and ETC activity
7. Increased formation of free radicals and lipid peroxidation
8. Decreased pools of alpha-KG and glutamate in brain (need AKG for TCA cycle, need glutamate for GABA)
9. Treatments:
10. low protein/high carb diet
11. levulose, which gets metabolized to acidic products; lower pH promotes NH4 excretion
12. antibiotics to kill NH4 producing bacteria
13. sodium benzoate/sodium phenylbutyrate promote N excretion

**Urea cycle disorders**: all have potential for neurological damage or death if not recognized early. Most have symptoms which include an excess of the deficient enzyme’s substrates

**Hyperammonenia type 1 (disorders in step 1 of urea cycle!)**

**CPI deficiency –** treat with arginine

**N-acetylglutamate deficiency –** treatment with carbamoyl glutamate

**Hyperammonenia type 2 (disorder in step 2!) = ornithine transcarbamylase deficiency –** treatment with low protein/high carb diet plus benzoic or phenylacetic acid to treat NH4 intoxication

**Argininosuccinate synthetase deficiency -** treatment with Arg

**Argininosuccinate lyase deficiency –** treatment with Arg

**Arginase deficiency –** treatment with low protein diet with essential AA minus Arg

**AA Metabolism disorders:**

**Branched ketoaciduria (Maple syrup disease)**- deficient in BCKAD. Accumulate alpha-ketoacids (which come from Val/leu/Iso). Alloisoleucine is diagnostic, mental retardation. 3 components of enzyme complex - Type 1A: E1 alpha subunit; type 1B: E1 beta subunit; Type II: E2; type 3: E3. Classic MSUD –lethargy, alternating hypo/hypertonia, less than 2% BCKAD activity. Intermediate – up to 30% activity. Intermittent – later onset, stress can trigger sx. Thiamine responsive: similar sx as intermediate, treat with low protein diet.

**Alkaptonuria –** defect in homogentistate oxidase (in Phe metabolism). Polymerized homogentistic acid leads to black urine (after prolonged rxn with O2), arthritis, calcifications in heart/urine tract, red skin

**B12 (coenzyme for methionine synthase and methylmalonyl-CoA mutase) deficiency – Pernicious anemia.** results from faulty absorption due to lack of glycoprotein intrinsic factor in stomach.

**Homocystinuria –** deficiency in cystathionine B-synthase (in Met metabolism). Ectopia lenitis (eye), osteoporosis, mental retardation, vascular clotting. Homocysteine forms cytotoxic and immunogenic products. Treatment with B vitamins (if responsive) or diet of –Met, +Cystine/Betaine (if vitamin unresponsive).

**Phenylketonuria -**  1/45 caucasians. Defective phenylalanine hydroxylase (phe -> tyr) gene. Mental retardation, epilepsy, strange posture, brain calcification, mousy odor, eczema. Treatment with -Phe/+Tyr diet

**Isovaleric Acidemia –** defects in isovaleryl-CoA dehydrogenase (IVA). Treatment: protein restriction, supplement with carnitine and glycine, which bind isovalerate to turn into nontoxic product. First type: vomiting, dehydration, acidosis. Second type: chronic/intermittent. lethargy progressing to coma, dirty sock odor, exacerbated by stress.

**Methylmalonic aciduria; proprionic aciduria –** Defects in MM-CoA mutase and proprionyl-CoA carboxylase. Different defective enzymes but same sx/tx. Accumulation of toxic metabolites, especially proprionate. Similar metabolite pattern in multiple carboxylase deficiency which affects biotin-dependent enzymes. Impaired mitochondrial energy production. Metabolic decompensation affects glycolysis, urea cycle (elevated ammonia), carnitine synthesis. Vomitting, weight loss, refusal to feed, abnormal movements, hypotonia, lethargy, seizures, coma if not treated promptly. Large anion gap, ketonuria, anemia, leukopenia. Affects brain, kidney, heart

**Nonketotic hyperglycinemia –** defects in glycine cleavage system, esp glycine synthase (which catabolizes Gly/Ser). 80% of mutations in P-protein, 20% in T-protein. Severe forms include lethargy vomiting, convulsions, loss of reflexes, death before 5 years. Origins of neuropathies: Gly receptors on both inhibitory neurons and NMDA (Glu) receptors, abnormal metabolism of tetrahydrofolate derivatives interferes with DNA precursors, remethylation of methionine. Therapy: Diazepam, ketamine, dextromethorphan reduce NMDA activity; sodium benzoate promotes Gly excretion; phenobarbital for seizures

**AA Transporter defects –** most have many different possible mutations

**Cystinosis –** defect in lysosomal cystine transporter. Deposition of cystine crystals in tissue. Death from renal failure. Photophobia, polyuria, hypothyroidism, impaired cognition. Treat with cysteamine.

**Cystinuria –** defect in transporter for cationic AA and cystine (apical side). elevated cystine in urine. Forms hexagonal cystine crystals in kidney tubules. Treatment: hydration, increase pH of urine using citrate or bicarbonate, reduction in cystine and Methionine intake, cystine-reactive drugs: Thiopronin, penicillamine, a-mercaptoprionylglycine. Type A: mutation in heavy chain (membrane-binding) Type B: mutation in light chain (transporter). Various mutations exist and vary in severity between both subunits. A/B also possible.

**Hartnup Disorder –** defects in Na-dependent neutral amino acid transportersTransporter associates with Collectrin (membranous protein trafficker) and ACE2 (vasodilator, converts angiotensin I/II to angiotensin 1-9/1-7). Photosensitive dermatitis, neurological problems, elevated urinary neutral AAs. Lack of Trp uptake leads to most symptoms because Trp is a precursor for nicotinamide and serotonin. Severity is influenced by diet. Hartnup includes kidney form, in which transporter does not associate with collectrin, and small intestinal form, in which transporter cannot associate with ACE2.

**Lysinuric protein intolerance –** recessive defect in basolateral transporter (SLC7A7 or LAT1) for cationic AAs. Defective uptake of Lys, Arg, Orn in SI and kidney. Lack of arginine leads to urea cycle derangement, which increases plasma ammonia. Patients develop aversion to proteins at early age. Stunted growth, enlarged liver and spleen, hypotonia, osteoporosis. Treatment: sodium benzoate/phenylbutarate to excrete nitrogen; citrulline to promote urea cycle; protein-restricted diet

**Sildenafil (Viagra) –** inhibitor of cGMP-specific PDE5 (found in heart/penis) which converts cGMP to GMP. Opens blood vessels for nice boners.

Maltese

**Diabetes Mellitus type I (juvenile) –** pancreas does not produce insulin. Can’t use glucose, high adipose lipolysis, AcCoa Carboxylase stays low.

**Type II (adult onset) –** insulin produced but tissues are resistant to its effects. Leads to high blood glucose which stimulates more insulin production. Reduced uptake of glucose also leads to gluconeogenesis, compounding the problem. Untreated diabetics are susceptible to ketoacidosis. Late-stage: pancreas becomes unresponsive to high glucose, stops making insulin. Obesity is a cause because large adipocytes release excess FA and resistin which interfere with function of the insulin receptor

**Respiratory distress syndrome –** lack of lung surfactant (high in phosphoglycerides). Cannot keep alveoli open. Therapy – using synthetic surfactant and partial liquid ventilation

**Tay-Sachs disease –** defect in hexosaminidase A (lysosomes cannot degrade gangliosides). Neuropathy, blindness, deafness, paralysis, death by age 3

**Gaucher’s disease –** deficiency in glucocerebrosidase (ceremide->glu). 3 types, 1 is most common. anemia, easy bruising, hypertrophy of liver/spleen, weak bones. Onset varies throughout life

**Niemann-pick disease –** deficiency in sphingomyelinase (ceremide->phosphatidyl choline). enlarged liver/spleen, retardation, anemia. Early onset, death before 3.

**Aspirin –** permanently inactivates cyclooxygenase (COX-1/2) aka prostaglandin synthase, inhibiting production of prostaglandins. Also inhibits TXA2 (thromboxane), which stimulates platelet aggregation

**Ibuprofen –** blocks the active site of COX-1/2. Same effects as aspirin.

**New generation NSAIDs (eg Celebrex, Vioxx)** – block only COX-2 which is induced with inflammation (COX-1 helps maintain normal functions). Less negative side effects.

**Acetaminophen –** reversibly inhibits COX-3 (only in brain). Thus reduces fever and pain but lacks anti-inflammatory/clotting effects

**Lovastatin (mevacor, Zocor, crestor, Lipitor)** – competitive inhibitors of HMC-CoA reductase. Lower cholesterol production.

**Questran, Colestipol, cholestyramine –** sequestrants which prevent bile reabsorption. Lowers cholesterol by redirecting it to synthesize bile.

**21-Hydroxylase deficiency –** enzyme needed for glucocorticoids and mineralcorticoids. Increased secretion of ACTH by ant. Pit. Hyperplasia, accumulation of pregnenolone, progesterone, and androgens. Lack of bone mineralization (short stature), loss of Na in urine, hypotension. Treatment: hormone replacement.

Manning

**Defective enzymes of glycogen storage:**

**Von gierke** disease: G 6-Pase

**Anderson** disease: branching enzyme->long glycogen

**McArdle** disease: muscle glycogen phosphorylase->excessive glycogen in muscle

**Pompe** disease: lysosomal glucosidase. Buildup of glycogen in muscles.

Goodridge

**Alli (Orlistat)** – anti-obesity. Inhibits pancreatic lipase. Causes intestinal problems, making patients averse to fat.

**Benecol and Promise –** margarines contain plant stanol esters/sterols which inhibit uptake of cholesterol into micelles and inhibit cholesterol esterase

**Ezetimibe (Zetia) –** inhibits enterocyte cholesterol transporter (NPC1L1)